REMARKS

Applicants have submitted herewith a substitute specification that contains formatting changes only. As admended, the newly formatted specification contains tables that comply with the font requirements set forth in 37 C.F.R. § 1.58(c).

Applicants have cancelled Claim 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide of SEQ ID NO: 12. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed October 4, 2004. For the reasons set forth below, Applicants respectfully traverse.

Substitute Specification

Applicants submit herewith a substitute specification. The PTO has objected to the original specification, since the font size of the tables does not meet the minimum requirements set forth in 37 C.F.R. § 1.58(c). The formatting of the specification has been corrected and replacement of the current specification with the substitute specification is respectfully requested.

Corrected PTO -1449

Applicants submit herewith a corrected Form PTO -1449. The original form contained a typographical error in the patent number of Jacobs. The number should be 5,536,637, not 5,546,637.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-6 as lacking a specific and substantial, or well-established utility. The PTO asserts that there is no physiological or clinical significance of the polypeptide of SEQ ID NO: 12 (PRO300). The PTO also states that PRO300 has no known structural or functional relationship to a well-described family of known proteins, and that the polypeptide lacks utility. The PTO states that because the polypeptide does not have utility, then antibodies that bind it also lack utility. One of the asserted utilities for the claimed antibodies is use as a diagnostic tool based on the data that PRO300 cDNA is more highly expressed in normal lung compared to lung tumor. The PTO has rejected this utility, maintaining that there is no disclosure of a disease or disorder associated with PRO300, and thus detection of PRO300 is not a substantial and specific utility. The PTO also states that because PRO300 lacks utility, there is no substantial utility for use of antibodies to purify PRO300. The PTO also states that the specification lacks guidance about which type of disease or disorder PRO300 causes or how its involvement could lead to treatment, and therefore the use of PRO300 in a screen for drugs would require further experimentation. The PTO also notes that the specification discloses that the cDNA encoding PRO300 is more highly expressed in normal lung tissue as compared to lung tumor. However, the PTO states that because the specification does not disclose relative or absolute levels of expression, the data is too sparse to confer utility upon the polypeptides encoded by the cDNA's as tumor markers. The PTO further argues that even if the encoding polynucleotide had utility as a tumor marker, the encoded polypeptide and antibodies that bind it would not have such utility because there is no reason to suspect that the polypeptide levels in normal lung tissue versus lung tumor correlate with the differential cDNA levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the

burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO300 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO300 polypeptide in normal lung tissue compared to lung tumor is insufficient because it does not disclose relative or absolute levels of expression of the cDNA encoding PRO300.

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed antibodies. Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The fact that the cDNA encoding PRO300 is more highly expressed in normal lung compared to lung tumor renders it useful as a diagnostic tool for cancer since it can be used as a

molecular marker for cancer. As discussed below, this fact leads to utility for the encoded polypeptides and their antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that there is no reason to suspect that PRO300 is more highly expressed in normal lung tissue compared to lung tumor.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 4). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Mr. Grimaldi and Dr. Polakis and the cited textbook establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO300 mRNA is expressed at a higher normal lung tissue compared to lung tumor tissue, the PRO300 polypeptide will also be expressed at a higher level in normal lung tissue compared to lung tumor tissue. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool, as would its antibodies. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of claimed antibodies as a cancer diagnostic tool.

The Claimed Antibodies would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO300, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 6). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertions that there is no disease or disorder that is disclosed as being associated with PRO300. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention."

M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO831 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data that show that the gene encoding the PRO300 polypeptide is more highly expressed in normal lung tissue compared to lung tumor tissue. These data are strong evidence that the PRO300 polypeptide is associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO300 polypeptide with a specific disease. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides and their antibodies.

Conclusion

The PTO has asserted various arguments why PRO300 and the claimed antibodies lack substantial utility: (1) there is no known physiological or clinical significance of PRO300; (2) there is no known disease or disorder associated with PRO300, or guidance as to how PRO300 could lead to a treatment; (3) there is no guidance as to how information regarding differential gene expression levels can be used; (4) there is no disclosure regarding absolute or relative levels of expression of the gene encoding PRO300 in normal lung compared to lung tumor; and (5) that differential expression of the claimed nucleic acids does not necessarily correlate with differential expression of the encoded polypeptides. Applicants have addressed each of these arguments in turn.

First, Applicants have pointed out that the data in Example 18 establish a physiological and clinical significance for PRO300 because the gene encoding PRO300 is differentially expressed in lung tumor cells compared to normal lung tissue. Applicants have provided a declaration stating that given the relative difference in expression levels of the nucleotides in the instant invention, the claimed antibodies have utility as cancer diagnostic tools. The fact that the levels of expression of the gene encoding PRO300 are different in normal lung tissue versus lung tumor provides the bases for the utility of the claimed antibodies. This is not a general utility that would apply to the broad class of polypeptides or antibodies that bind them.

Applicants have also provided a declaration stating that the data in Example 18 reporting higher expression of the PRO300 gene in normal lung compared to lung tumor are real and significant.

Finally, Applicants have presented the declarations of two experts in the field along with supporting references that establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO300 polypeptide, and thus antibodies that bind to PRO300, have utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO300 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial and specific or well-established utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claim 6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "specifically binds", stating that it is a term of degree for which no guidance is present, thus rendering the claim indefinite. The PTO states that the specification does not provide guidance as to what is encompassed by "specifically binds" as opposed to "binds".

Claim 6 has been canceled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning – it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO: 12) but do not substantially bind to any other polypeptides. Since claim terms should be given their ordinary, art-recognized meaning, Applicants submit the present rejection is misplaced, and request that it be withdrawn.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-6 as anticipated under 35 U.S.C. § 102(b) by Eaton *et al.* (WO 01/16318), published in March 2001. Presumably, this rejection is based on the PTO's determination that the disclosure to which priority is claimed fails to meet the requirements of §§101 and 112, first paragraph, and thus setting the priority at the instant filing date, May 1, 2002. The PTO asserts that WO 01/16318 teaches the polypeptide of SEQ ID NO: 12, which is 100% identical to SEQ ID NO: 12 of the instant application, as well as antibodies that bind to the polypeptide of SEQ ID NO: 12.

To anticipate under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Under 35 U.S.C. § 120, an applicant is entitled to the benefit of the filing date of an earlier filed application that discloses the same invention in the manner provided by 35 U.S.C. § 112, first paragraph, provided that the applicant properly claims priority to the earlier application. In a preliminary amendment filed on September 3, 2002, Applicants made specific reference to WO 01/16318, claiming priority thereto. WO 01/16318 contains the same disclosure regarding PRO300 and its utilities as the instant application,

including the data in Example 18. For the same reasons detailed above in the Remarks addressed to the rejections under 35 U.S.C. §§ 101 and 112 in the instant response, Applicants submit that WO 01/16318 is enabling for the claimed invention. Therefore, because Applicants have properly claimed priority to WO 01/16318, and because WO 01/16318 satisfies the requirements of 35 U.S.C. § 112, Applicants are fully entitled to the benefit of the filing date of WO 01/16318. Thus, Applicants respectfully request that the PTO reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Jan. 3, 2005

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